

Donner Laboratory and the Origins of Experimental Radiation Therapy: A Historical Survey of High-Risk Innovation in Cancer Treatment

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During the mid-20th century, a remarkable convergence of physics and medicine took place at the Donner Laboratory at the University of California, Berkeley. Founded by Dr. John H. Lawrence, a pioneer in nuclear medicine, the lab became the first in the world to apply cyclotron-produced isotopes and particle beams in the treatment of human disease. Long before terms like “precision oncology” and “targeted therapy” became common, researchers at Donner were experimenting with radioactive isotopes, neutron beams, and even heavy ions to selectively destroy cancer cells while minimizing harm to healthy tissue. These efforts were not only scientifically bold but also ethically complex, occurring in an era when concepts such as informed consent were still emerging. This paper surveys the laboratory’s most experimental approaches—from boron neutron capture therapy to magnetic targeting—while also considering their legacy in today’s proton therapy, carbon ion treatment, and internal radiation techniques. By revisiting these high-risk, high-reward innovations, we gain insight into how the intersection of ambition, curiosity, and responsibility helped shape the future of cancer therapy.

Keywords: Donner Laboratory, radiation therapy, nuclear medicine, proton therapy, carbon ion therapy, heavy ion therapy, neutron beams, boron neutron capture therapy, radioactive isotopes, cancer treatment history, John H. Lawrence, ethical experimentation, medical cyclotron, internal radiation, magnetic targeting>
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Note: The UC Berkeley Biophysics Group was headquartered at Donner Laboratory during the time I was working on my Ph.D. in Biophysics (1975 – 1981).

1. Introduction

The emergence of nuclear medicine in the mid-20th century represents one of the most transformative periods in the history of biomedical science. Catalyzed by the development of nuclear physics and radiochemistry, this field bridged previously disparate disciplines—physics, biology, and medicine—into a new scientific and clinical paradigm. The possibilities for diagnosis and treatment using radioisotopes and subatomic particles created unprecedented opportunities to investigate and manipulate physiological processes at the molecular and cellular level. Nowhere was this interdisciplinary vision more fully realized than at the Donner Laboratory, founded at the University of California, Berkeley.

The Donner Laboratory was established in the late 1930s under the leadership of Dr. John H. Lawrence, a trained physician and the younger brother of Ernest O. Lawrence, Nobel laureate and inventor of the cyclotron. With support from the Donner family, the laboratory was formally opened in 1942. It was conceived as a facility where advances in particle physics could be directly translated into human medicine. John Lawrence saw the cyclotron not only as a tool for atomic exploration, but as a potent source of therapeutic agents—producing radioactive isotopes that could be administered to patients or used in conjunction with targeted beam therapies.

From its inception, the Donner Laboratory was guided by a bold and experimental research agenda. It sought to develop therapeutic applications of radioisotopes, deliver high-energy particle beams with surgical precision, and use nuclear tracers to study metabolic and physiological function in vivo. This vision represented a profound departure from classical medicine: here, the invisible and the atomic became accessible tools for the clinician.

One of the laboratory's first and most notable breakthroughs came with the use of radioactive phosphorus-32 (^{32}P) to treat polycythemia vera and leukemia. This work, initiated in the 1930s, set the stage for decades of research into how systemically administered isotopes could selectively target proliferating cells. Alongside these efforts, the lab also pursued external beam therapy using neutrons, protons, and later heavy ions—innovations that would lay the

groundwork for the proton and carbon-ion therapies used in today's oncology centers.

Throughout its early history, the Donner Laboratory functioned as both a research hub and a clinical site. Patients were treated on-site, sometimes with therapies that were considered highly experimental by contemporary standards. Yet it was this very willingness to explore the unknown that enabled the lab to become a world leader in radiation medicine. As a result, the Donner Laboratory not only contributed foundational knowledge to the science of nuclear medicine, but also shaped the ethical and clinical frameworks that govern high-risk biomedical innovation.

In this paper, we explore the more exotic and pioneering experiments undertaken at Donner, examining their scientific rationale, clinical impact, and ethical implications. By revisiting these early ventures at the intersection of physics and medicine, we gain a deeper understanding of how radiation therapy evolved—and how the lessons of the past continue to inform the challenges and promises of cancer treatment today.

2. The Birth of Medical Isotope Therapy

The birth of medical isotope therapy marked a decisive turning point in the treatment of cancer and hematological disorders. In the early 20th century, the prevailing approaches to cancer therapy were largely limited to surgical excision and rudimentary forms of radiation using external X-rays. However, the development of the cyclotron by Ernest O. Lawrence in the 1930s opened an entirely new frontier: the ability to artificially produce radioactive isotopes for therapeutic use. Among these, phosphorus-32 (^{32}P) emerged as one of the first isotopes used in the systemic treatment of disease—a breakthrough pioneered by Dr. John Lawrence and his team at the Donner Laboratory.

Phosphorus-32, a beta-emitting radioisotope, was produced by bombarding sulfur with neutrons in the Berkeley cyclotron. Its biological utility lay in its chemical similarity to stable phosphorus, an essential element in DNA, RNA, and other

critical biomolecules. When introduced into the human body, ^{32}P is readily incorporated into rapidly dividing cells, particularly in the bone marrow. This property made it especially effective against disorders characterized by excessive cellular proliferation, such as leukemia and polycythemia vera.

In 1936, John Lawrence administered ^{32}P to a patient suffering from polycythemia vera, a disease involving the overproduction of red blood cells. The treatment, which involved systemic injection of the isotope, resulted in a measurable reduction in red blood cell count and symptomatic relief—a result that was nothing short of revolutionary. Soon after, ^{32}P was also used in patients with leukemia, where its affinity for rapidly dividing cells offered a means of slowing disease progression without the need for invasive procedures.

These early successes led to the expansion of radioisotope therapy to include other isotopes, such as iodine-131 (I-131) and gold-198 (Au-198). Iodine-131, developed at Oak Ridge and later adopted at Berkeley, proved ideal for targeting the thyroid gland due to its natural uptake of iodine. It rapidly became a standard treatment for hyperthyroidism and differentiated thyroid cancer. Gold-198, a gamma emitter, was used in the form of colloidal solutions or sealed sources implanted directly into tumors—an early form of brachytherapy. Though its use was limited by logistical and safety challenges, it illustrated the broader potential of isotope-based localization strategies.

One of the defining features of this era was the transition from localized, external radiation to internal, systemic therapy. For the first time, clinicians could administer radiation that would selectively concentrate in diseased tissue, delivering therapeutic effects from within the body. This paradigm shift also enabled physicians to visualize disease processes using isotopic tracers—a practice that eventually evolved into modern nuclear imaging techniques such as PET and SPECT.

However, these early interventions were not without significant ethical complexities. Patients often received treatments that were experimental in nature, with limited understanding of long-term risks. Informed consent, as defined by contemporary standards, was often lacking or minimal. In many cases,

patients suffering from terminal diseases were enrolled in isotope therapy studies with the dual intent of therapeutic benefit and scientific exploration. Though the intentions of the researchers were largely humanitarian, the asymmetry in knowledge between physician and patient raised difficult questions that continue to inform medical ethics today.

Early patient responses to radioisotope therapy were mixed but frequently hopeful. For those with few or no treatment options, the prospect of systemic radiation offered a lifeline. Remissions were observed in some leukemia patients, and sustained improvements were seen in those with polycythemia vera. In other cases, the effects were less dramatic, and toxicity could be severe. Nonetheless, the work done at Donner Lab in this period laid the essential foundation for the field of nuclear medicine. It demonstrated that disease could be treated not just by cutting or irradiating from the outside, but by altering it from within—using isotopes engineered at the atomic level for therapeutic precision.

Thus, the birth of medical isotope therapy was not just a technical milestone but a conceptual leap. It redefined the boundaries of medicine and physics, offering a glimpse of a future in which targeted, individualized treatments could be constructed from the fundamental building blocks of matter. It was, in essence, the first step toward the modern vision of precision oncology.

3. Neutron Beam Therapy and Pituitary Interventions

The application of neutron beam therapy at the Donner Laboratory marked one of the earliest efforts to harness high-linear energy transfer (high-LET) radiation for therapeutic purposes in humans. This approach, innovative and high-risk, stood at the intersection of experimental physics and clinical medicine. While gamma rays and X-rays had already found their place in the radiotherapy arsenal, neutrons—uncharged, high-mass particles—offered a new dimension. With significantly higher relative biological effectiveness (RBE), neutron radiation had the capacity to induce complex, irreparable damage to DNA, especially in slowly proliferating tissues and radioresistant tumors. This potency came with both promise and peril.

The Berkeley cyclotron, originally built for nuclear physics experiments, was repurposed to generate a therapeutic neutron beam by bombarding beryllium targets with accelerated deuterons. This technique produced high-energy neutrons capable of penetrating deep into tissue while delivering concentrated damage to cellular structures. John Lawrence and his team recognized the therapeutic potential of such a beam, particularly for disorders of the pituitary gland, which is nestled at the base of the brain and plays a central role in regulating the endocrine system.

Two of the primary diseases targeted were acromegaly and Cushing's disease, both caused by hyperactive pituitary adenomas that secrete excessive amounts of growth hormone or adrenocorticotrophic hormone (ACTH), respectively. These hormonal imbalances lead to profound physiological changes—acromegaly results in abnormal growth of bones and soft tissues, while Cushing's disease causes severe metabolic and immune disturbances.

Surgical approaches to these tumors were extremely limited at the time. Neurosurgical techniques lacked the precision and safety to reliably access the pituitary without high mortality. Neutron beam therapy offered a non-invasive alternative: by directing the beam transnasally or laterally through the skull, the team could irradiate the pituitary gland without opening the cranium. The goal was to reduce or eliminate hormone secretion by selectively damaging the adenomatous tissue.

Initial results were compelling. Patients with acromegaly showed regression of physical symptoms and stabilization of growth hormone levels. In cases of Cushing's disease, ACTH levels fell, and the associated symptoms—weight gain, hypertension, immune suppression—began to abate. These were among the first documented successes in functional endocrine ablation via radiation, a concept that would later be refined into more precise radiosurgical interventions.

However, the very potency of high-LET neutron radiation posed significant challenges. While effective at halting hormone secretion, neutron beams were far less discriminating than modern photon or proton therapies. The absence of electric charge meant that neutrons interacted stochastically with tissue, and their

dose deposition was less controllable than charged particles. As a result, collateral damage to surrounding brain tissue was a real risk. Some patients experienced cognitive decline, visual disturbances, or vascular complications following treatment—side effects that limited broader adoption of the technique.

This tension—between therapeutic efficacy and unintended harm—defined much of the early era of neutron therapy. The concept of precision in radiation therapy was still nascent; treatment planning lacked the detailed imaging and dose modeling that characterize modern radiotherapy. Beam shaping, collimation, and shielding were rudimentary by today's standards, making it difficult to confine the neutron flux exclusively to the target tissue.

Nevertheless, these early pituitary interventions established a precedent for the integration of particle physics into clinical endocrinology and oncology. They demonstrated that deep-seated, inaccessible structures could be therapeutically modulated without surgery, using energy delivered across space by subatomic particles. The insights gained—about dosimetry, tissue response, and therapeutic thresholds—contributed directly to the eventual development of stereotactic radiosurgery, proton therapy, and heavy-ion beam therapy.

In hindsight, neutron beam therapy at Donner Lab was a bold and formative experiment. It challenged the limits of available technology, raised ethical questions about patient risk in experimental treatment, and delivered real benefits to individuals who had no other medical options. Most importantly, it laid the conceptual and technological groundwork for a new model of medicine: one in which disease is treated not by mechanical intervention alone, but by the careful deployment of fundamental physical forces.

4. Heavy Ion and Exotic Beam Therapies

The evolution of particle beam therapy at the University of California, Berkeley took a major leap forward in the 1970s with the transition from neutron beams to heavy ion therapy, particularly the use of helium and carbon ion beams. This advancement was largely enabled by the construction of the Bevalac, a hybrid

accelerator formed by coupling the Bevatron (a high-energy synchrotron) with the SuperHILAC (Heavy Ion Linear Accelerator). Located at Lawrence Berkeley Laboratory, the Bevalac was originally built for nuclear physics experiments but soon became a unique platform for medical innovation—capable of accelerating a wide range of ions, from protons to heavier nuclei such as carbon and neon.

This shift from neutron therapy to heavy ions was driven by both physical and biological insights. Heavy charged particles have distinct advantages over neutrons and conventional photons in cancer therapy. Unlike photons, which deposit energy exponentially along their path, or neutrons, which scatter unpredictably, heavy ions deliver most of their energy at the end of their path in a sharp peak known as the Bragg peak. This allows for maximum energy deposition within the tumor and minimal damage to surrounding healthy tissue, a crucial benefit when treating tumors located near vital structures.

Additionally, heavy ions possess a high linear energy transfer (LET), enabling them to create dense ionization tracks that cause complex, clustered DNA damage—particularly effective against radioresistant tumors. Whereas low-LET radiation often permits cells to recover through DNA repair, the damage induced by high-LET ions is far more difficult to repair, leading to more reliable tumor cell death.

One of the most successful clinical applications of heavy ion therapy at the Bevalac was the treatment of ocular melanomas, which are notoriously difficult to treat without sacrificing vision. Conventional radiotherapy often leads to significant radiation damage to the optic nerve and retina. Helium ion beams, on the other hand, could be finely collimated and precisely delivered to the tumor with minimal exit dose, allowing for tumor ablation while preserving surrounding healthy eye structures. More than 300 patients with ocular melanoma were treated successfully at Berkeley between the late 1970s and early 1990s, many of whom retained useful vision in the treated eye—a remarkable outcome at the time.

In addition to ocular tumors, deep-seated tumors such as those located in the head and neck, spine, and pelvis were also targeted using carbon and neon ion beams. These locations typically pose challenges for surgery and conventional

radiotherapy due to their proximity to sensitive structures like the brainstem, spinal cord, or critical organs. Heavy ion therapy allowed clinicians to pursue aggressive treatment regimens with a reduced risk of collateral damage. Tumors that had recurred after multiple courses of conventional radiation—often considered untreatable—were given another opportunity for control using heavy ions.

Outcomes from these treatments were encouraging, particularly in terms of local control, tumor regression, and symptom relief. In several patient cohorts, local control rates exceeded those of standard photon therapy, especially for tumors classified as resistant to other modalities. Importantly, some patients with previously inoperable or recurrent tumors achieved long-term remission or even apparent cures. These results attracted international attention and helped to establish the biological and clinical rationale for expanding heavy ion therapy beyond Berkeley.

Yet despite the clear scientific and clinical promise, heavy ion therapy at the Bevalac remained experimental. The facility itself was not optimized for routine clinical use: treatment times were long, patient positioning was challenging, and the overall infrastructure lacked the automation and safety systems found in modern proton or photon centers. Moreover, the cost of maintaining such a large accelerator for limited clinical throughput was significant, and by the early 1990s, the program was discontinued as funding priorities shifted.

Nevertheless, the Berkeley experience laid the foundation for the development of dedicated heavy ion therapy centers in Europe and Asia. Japan's National Institute of Radiological Sciences (NIRS) and Germany's Heidelberg Ion-Beam Therapy Center (HIT) were directly inspired by the work at the Bevalac. These centers improved upon Berkeley's pioneering model by integrating state-of-the-art imaging, computer-controlled beam delivery, and patient-specific treatment planning.

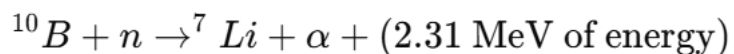
Today, carbon ion therapy is an accepted clinical modality in several countries, and its use is growing worldwide. Its heritage can be traced directly to the experiments conducted at Berkeley, which demonstrated not only the feasibility of heavy ion

treatment, but its profound potential to transform radiation oncology. The Bevalac's legacy lies not merely in its technological achievements, but in its bold attempt to reimagine cancer treatment using the full spectrum of the physical sciences. It proved that even the heaviest of particles, when directed with care, could offer light and hope to patients with the darkest diagnoses.

5. Boron Neutron Capture Therapy (BNCT)

Boron Neutron Capture Therapy (BNCT) represents one of the most conceptually elegant and biologically selective forms of cancer radiotherapy ever developed. First proposed in the 1930s and later refined throughout the mid-to-late 20th century, BNCT was explored extensively at institutions like UC Berkeley's Donner Laboratory due to their access to research reactors and neutron sources. Unlike traditional radiation therapies that rely on indiscriminate energy deposition across tissue volumes, BNCT is inherently a binary therapy—its therapeutic effect is only realized when two separate conditions are simultaneously met: (1) selective accumulation of boron-10 in tumor cells and (2) targeted irradiation with low-energy (thermal or epithermal) neutrons. Only when these two criteria are fulfilled at the same location does the cytotoxic effect occur.

The underlying mechanism of BNCT hinges on the nuclear reaction between B10 and low-energy neutrons:



This reaction produces a high-energy alpha particle and a recoiling lithium-7 nucleus. Both products have very short path lengths—on the order of 5–9 micrometers—approximately the diameter of a single cell. This means that the radiation damage is entirely localized to the cell that contains the boron atom. Surrounding tissues, even those just micrometers away, receive negligible exposure. This in situ destruction makes BNCT especially attractive for treating infiltrative or diffuse tumors like glioblastoma multiforme, where traditional

surgery or radiation cannot eliminate cancer cells without compromising surrounding healthy brain tissue.

Achieving this cellular selectivity, however, is predicated on the ability to deliver a sufficiently high concentration of boron-10 to the tumor without affecting normal cells. Early boron delivery agents included boric acid, boronophenylalanine (BPA), and sodium borocaptate (BSH). These compounds had varying affinities for tumor cells, and many early trials struggled with inconsistent uptake or poor tumor-to-normal tissue ratios. One major challenge was ensuring that enough boron accumulated in all malignant cells, including those in hypoxic or poorly vascularized regions, while minimizing background accumulation elsewhere. Researchers at Berkeley and other centers experimented with modifying chemical structures, using carrier molecules, and exploiting amino acid transport systems upregulated in cancer cells to improve targeting.

Another formidable challenge lay in the neutron source itself. BNCT requires a beam of epithermal neutrons that can penetrate tissue to reach deep-seated tumors but slow down to thermal energies by the time they interact with boron in the target cells. The ideal neutron spectrum must be carefully tailored, which typically requires access to a nuclear reactor or a specially configured particle accelerator. Donner Laboratory and its collaborators were among the few institutions in the United States with the infrastructure to conduct such research, but even so, clinical application was constrained by the scarcity of suitable neutron sources.

Throughout the latter half of the 20th century, BNCT was applied in several clinical trials, particularly for brain tumors and recurrent head and neck cancers. One of the most promising areas was in treating glioblastoma, a lethal and highly invasive brain tumor for which conventional therapies offered limited survival. BNCT was used as an adjunct to surgery, often in patients who had exhausted other options. Case studies documented partial responses and, in some instances, temporary stabilization of disease. However, the variability in boron uptake and the logistical difficulty of neutron delivery meant that outcomes were inconsistent. Some patients experienced clear therapeutic benefit; others suffered side effects such as

brain edema or radiation necrosis, typically linked to poor spatial control of neutron exposure or uneven boron distribution.

Despite these therapeutic limitations, BNCT remains a valuable proof of concept for biologically selective radiation. Its strength lies in the precise cellular targeting enabled by the boron-neutron interaction, and its weakness lies in the complexity of implementation—from boron pharmacokinetics to neutron beam optimization. The field has experienced a revival in recent years due to the development of accelerator-based neutron sources, which promise greater accessibility than traditional nuclear reactors. Novel boron delivery agents, including nanoparticle-based formulations and boronated antibodies, are also being investigated to overcome the pharmacological barriers that hindered early applications.

The legacy of BNCT at institutions like Donner Laboratory lies not in its widespread clinical adoption but in its demonstration of what is physically and biologically possible. It advanced the idea that radiation could be made intelligent—not merely targeted at tissues or organs, but at specific cells, even subcellular compartments. In an era increasingly focused on precision oncology and molecular targeting, BNCT stands as a conceptual forerunner, embodying the fusion of nuclear physics, chemistry, and medicine in pursuit of a highly localized and highly effective cancer therapy.

6. Radioactive Microspheres and Lymphatic Colloids

The development of radioactive microspheres and colloidal suspensions for internal radiotherapy represents a critical juncture in the evolution of precision-targeted cancer treatments. Emerging in the mid-20th century, particularly through research conducted at centers such as the Donner Laboratory, these techniques embodied the aspiration to confine radiation exposure to malignant tissues while sparing healthy structures—a goal that traditional external beam radiotherapy often struggled to achieve. Though experimental at the time, these methods laid the groundwork for modern therapies like Selective Internal

Radiation Therapy (SIRT), now widely used to treat liver tumors and other malignancies.

Microspheres, typically composed of glass, resin, or polymer materials, were engineered to be loaded with beta-emitting isotopes such as yttrium-90 (^{90}Y), gold-198 (^{198}Au), or phosphorus-32 (^{32}P). Once prepared, they were suspended in a carrier fluid and delivered directly into the vasculature feeding a tumor, often via catheterization of a major artery. The microspheres would then become lodged in the capillaries of the tumor, where their radioactive decay delivered a concentrated, localized dose of ionizing radiation. Because these particles were physically immobilized in the microvasculature and emitted low-penetration beta particles, radiation exposure to surrounding tissues was minimized.

One of the earliest and most effective applications of this technique was in the treatment of liver cancers, particularly hepatocellular carcinoma and metastatic colorectal cancer to the liver. The liver's unique dual blood supply—receiving arterial blood through the hepatic artery and venous blood through the portal vein—allowed for the selective targeting of tumor tissues, which tend to derive their blood primarily from the hepatic artery. By injecting radioactive microspheres into the hepatic artery, researchers could selectively irradiate the tumor while sparing the majority of the normal liver tissue, which is predominantly supplied by the portal vein.

This form of treatment, while primitive by modern standards, served as a precursor to Selective Internal Radiation Therapy (SIRT) or radioembolization, which uses ^{90}Y -labeled microspheres delivered via interventional radiology under advanced imaging guidance. The conceptual foundations for this modern procedure were laid decades earlier at laboratories like Donner, where the biological behavior of embolic agents and the dosimetric profiles of various isotopes were systematically investigated.

In parallel, researchers explored the use of radioactive colloids—suspensions of radioactive particles typically smaller than microspheres—for lymphatic cancers. These colloids were often injected directly into lymph nodes, body cavities, or tumor-infiltrated regions, where they would accumulate and deliver therapeutic

radiation. Colloids containing isotopes such as gold-198 or antimony-124 were used to treat Hodgkin's disease, pleural effusions caused by metastatic cancer, and other malignancies involving the lymphatic system.

The delivery methods varied depending on the target. In the case of liver cancer, intra-arterial catheterization was required, which demanded surgical precision and posed risks of misplacement or non-target embolization. For lymphatic applications, direct percutaneous injection or surgical access to lymph nodes was more common. Despite their experimental nature, these methods demonstrated a surprising degree of selectivity and efficacy, particularly in palliative settings where conventional therapy had failed or was contraindicated.

Safety profiles for radioactive microsphere and colloid therapy in this early era were cautiously optimistic but far from risk-free. Complications included unintended radiation to non-target tissues, vascular damage, embolic phenomena, and systemic leakage of the radiopharmaceuticals. In liver treatments, complications such as radiation-induced liver disease (RILD), gastrointestinal ulceration from reflux, and hepatic artery thrombosis were not uncommon. In lymphatic applications, the inflammatory response to colloids sometimes caused local fibrosis or delayed drainage. Nevertheless, the ability to deliver high radiation doses directly to malignancies with relative sparing of healthy tissues represented a considerable advancement in the therapeutic index.

These early experiences provided invaluable dosimetric and biological data that informed the eventual standardization and regulatory approval of internal radiotherapy systems. Researchers developed models of microsphere distribution, particle size optimization, and isotope half-life matching to better tailor the therapy to tumor characteristics and patient anatomy. Innovations in catheter design, nuclear imaging for verification of delivery, and radiobiological modeling all owe much to the groundwork laid in this experimental period.

In summary, the use of radioactive microspheres and colloids in internal radiation therapy represents a pioneering effort to achieve micro-scale precision in radiotherapy long before the advent of modern imaging and computing. By delivering therapeutic agents directly to the tumor microenvironment,

researchers at Donner Laboratory and similar institutions demonstrated that radiation could be confined not just to regions of the body, but to specific circulatory and lymphatic compartments, ushering in a new vision of how cancer might be confronted—particle by particle, from the inside out.

7. Experiments Involving the Blood-Brain Barrier

The treatment of central nervous system (CNS) tumors has long been constrained by one of the most formidable anatomical defenses in the human body: the blood-brain barrier (BBB). This selectively permeable barrier, composed of tight junctions between endothelial cells and supported by astrocytic foot processes, serves to protect the brain from toxins and pathogens—but in doing so, it also prevents many therapeutic agents, including most systemic chemotherapeutics and radiolabeled compounds, from reaching their targets within the brain parenchyma. During the mid-to-late 20th century, researchers at institutions like the Donner Laboratory began conducting experimental work aimed at temporarily and selectively breaching the BBB to allow the delivery of therapeutic isotopes and particle beams into the brain.

These investigations were motivated in large part by the dismal prognosis associated with aggressive brain tumors, particularly glioblastoma multiforme (GBM), an infiltrative astrocytic tumor known for its resistance to conventional therapy and poor five-year survival rates. Standard surgery often failed to achieve complete resection due to the tumor's diffuse boundaries, and systemic treatments were largely ineffective because of the BBB's filtering role. This created both the necessity and the opportunity for bold innovation.

One of the most widely explored techniques to bypass the BBB involved the use of hyperosmotic solutions, particularly mannitol, to transiently disrupt the tight junctions of the endothelial cells lining cerebral capillaries. When injected intra-arterially in high concentration, mannitol created an osmotic gradient that caused endothelial cells to shrink, thus loosening the tight junctions and allowing macromolecules—and in some cases, even radiolabeled compounds or

nanoparticles—to pass into the brain parenchyma. This process was reversible, typically restoring the integrity of the BBB within a matter of hours, which allowed for a narrow therapeutic window.

At Donner and collaborating facilities, mannitol-induced BBB disruption was followed by the administration of radioactive isotopes such as iodine-131, phosphorus-32, or boron-containing compounds in the context of boron neutron capture therapy (BNCT). In some protocols, the isotope was administered systemically following mannitol, while in others, it was delivered intra-arterially or intrathecally. The goal was to ensure that the radiopharmaceuticals, once denied access to the CNS, could now localize within tumor tissues that lay beyond the disrupted barrier.

Beyond isotope delivery, researchers also sought to use the BBB disruption strategy to enhance the penetration of particle beams. While neutron and proton beams could pass physically through the skull and reach intracranial targets, the biological effectiveness of certain compounds—such as boron agents in BNCT—still depended on their uptake within the tumor. Therefore, mannitol and similar agents were used to optimize the distribution of these compounds before irradiation, enhancing the selectivity and efficacy of beam-based approaches.

Implications for glioblastoma and other CNS tumors were significant, at least conceptually. The strategy opened new therapeutic avenues for deep-seated or surgically inaccessible tumors, including not just GBM but also primary CNS lymphomas and certain metastatic lesions. By overcoming the BBB temporarily, researchers could experiment with therapeutic agents whose efficacy had been established in peripheral tumors but were previously excluded from CNS application. Early case reports and pilot studies showed some tumor regression and symptomatic relief, though results were highly variable and depended on tumor location, size, vascularity, and the patient's overall condition.

However, these experimental strategies were not without risk. The transient opening of the BBB could inadvertently allow not only therapeutic agents but also systemic toxins, pathogens, or immune cells into the brain, increasing the potential for cerebral edema, infection, or autoimmune reactions. Some patients

experienced severe complications, including seizures, intracranial hemorrhage, or neuroinflammation. The precise control of mannitol infusion rate and concentration was critical, and the margin for error was narrow.

Moreover, achieving uniform delivery of therapeutic compounds across the entire tumor volume remained elusive, particularly in tumors with heterogeneous perfusion or necrotic cores. While mannitol could open the barrier locally, its effects were spatially and temporally limited, often leaving portions of the tumor untreated or underdosed. Additionally, the temporary nature of BBB disruption imposed strict time constraints on therapeutic delivery and irradiation scheduling.

Despite these limitations, the experiments involving BBB disruption at centers like the Donner Laboratory provided an invaluable proof of concept. They demonstrated that the brain's protective isolation could be selectively, safely, and temporarily bypassed under controlled conditions, enabling a new class of CNS-directed therapies. This work foreshadowed modern efforts involving focused ultrasound, receptor-mediated transcytosis, and nanoparticle-based drug delivery systems, all of which aim to navigate or modulate the BBB to enhance treatment of brain tumors.

In retrospect, the attempts to deliver isotopes and beams across the BBB represented a bold convergence of physiology, pharmacology, and radiation physics. While these experiments were largely investigational and often carried substantial risk, they signaled a critical shift in the conceptual landscape of neuro-oncology: from resignation in the face of the BBB to the idea that this barrier, like the tumor itself, could be challenged, manipulated, and ultimately overcome.

8. Magnetic Targeting and Experimental Concepts

Among the more unconventional avenues explored in mid-20th-century cancer therapy research—particularly by experimentalists associated with institutions like the Donner Laboratory—were early attempts at magnetic targeting: the idea that radioactive particles or therapeutic agents could be physically steered or concentrated within the human body using externally applied magnetic fields.

These concepts, though speculative and technologically ahead of their time, reflected the spirit of radical innovation that characterized much of the early work in radiation medicine.

The theoretical underpinnings of magnetic targeting rely on fundamental principles of classical electromagnetism: charged particles or magnetically responsive materials experience a force when subjected to magnetic fields, potentially allowing for spatial guidance through bodily fluids or tissues. If radioactive particles could be engineered to respond predictably to such fields, researchers hypothesized, they might be navigated directly to tumor sites, improving localization and reducing systemic exposure.

Early investigations into this idea focused primarily on two classes of agents:

1. Radioactive ferrofluids—colloidal suspensions of magnetic nanoparticles labeled with therapeutic isotopes, such as gold-198 (^{198}Au) or phosphorus-32 (^{32}P).
2. Paramagnetic microspheres or colloids—tiny magnetic beads or droplets embedded with radioactive material, potentially injectable into the vascular or lymphatic system.

In these experiments, once the agent was injected into the bloodstream or targeted region, powerful magnets—usually static electromagnets or rare-earth permanent magnets—were applied externally to the body to attempt to draw or hold the particles at the tumor site. Some theoretical designs even included rotating magnetic fields to “focus” the particles more precisely, much like a magnetic lens.

While these early efforts were intellectually bold, they faced significant practical limitations:

- Magnetic field strength and penetration: The human body presents a highly resistive and heterogeneous medium for magnetic field manipulation. The field strength required to steer particles over any significant distance through vascular networks or tissue matrices was far beyond the capability of mid-20th-century magnets, especially without harming the patient.

- Particle size and flow dynamics: Microspheres small enough to navigate blood vessels were often too small to respond strongly to practical magnetic fields, while larger particles could cause embolisms or be filtered out by the lungs or liver before reaching the intended site.
- Turbulent vascular flow: The circulatory system's dynamic, branching, and high-velocity nature made directed particle navigation exceedingly difficult. Even with advanced magnetics, precision control in this environment proved nearly impossible.
- Safety and distribution control: Ensuring that all or most of the radioactive particles reached the tumor without depositing elsewhere in the body was a major unresolved problem, particularly with radioactive decay occurring during circulation.

As a result, magnetic targeting never became a mainstream clinical tool in this era. However, the experimental work planted seeds that would reemerge decades later, buoyed by advances in materials science, computational modeling, and nanotechnology.

In contemporary research, magnetic targeting has found new life in the form of magnetic nanoparticles (MNPs), often made of iron oxide and coated with biocompatible polymers. These particles can be functionalized with tumor-seeking ligands (e.g., antibodies, peptides) and loaded with chemotherapeutic drugs or isotopes. In preclinical studies and some clinical trials, MNPs have been shown to improve the concentration of therapeutic agents at tumor sites, particularly in superficial tumors or organ-confined lesions like hepatocellular carcinoma.

One emerging field involves magnetic hyperthermia, in which MNPs are introduced into the tumor and then exposed to an alternating magnetic field, causing them to generate localized heat and kill cancer cells through thermal ablation. Similarly, MRI-guided drug delivery systems are being developed that use the imaging and magnetic manipulation capabilities of MRI machines to both track and direct therapeutic particles in real time.

Moreover, with the development of magnetically steerable catheters and microrobots, some researchers are exploring the possibility of navigating therapeutic payloads through difficult anatomical regions, such as cerebral vasculature or bronchial networks, by remote magnetic control. While these technologies are still in early stages, they illustrate how far the foundational ideas explored at places like Donner have evolved.

In summary, the concept of magnetic targeting, though largely unrealized during the era of classical nuclear medicine, exemplifies the creative intersection of physics and oncology that defined experimental programs like those at the Donner Laboratory. These early efforts, while technologically limited, were far from misplaced. They anticipated a future in which therapeutic delivery might one day be guided not just by anatomical imaging or biochemical targeting, but by the precise physical manipulation of matter within the human body—a vision that modern science is only now beginning to fulfill.

9. Ethical Reflections and Controversial Experiments

The pioneering era of nuclear medicine and radiation oncology, while marked by astonishing scientific progress, was also shadowed by complex and sometimes troubling ethical circumstances. The 1940s in particular witnessed a series of experiments—some publicly acknowledged only decades later—in which radioactive substances were administered to human subjects without proper consent. These activities occurred under the shroud of secrecy surrounding the Manhattan Project and the post-war atomic age, when the boundaries between military research, medical innovation, and human rights were not clearly delineated. While the Donner Laboratory at UC Berkeley played a leading role in the development of medical uses for radioisotopes, it is essential to distinguish its clinical research agenda from some of the more ethically controversial practices carried out at other facilities under federal authority.

The most infamous of the non-consensual radiation experiments took place not at Donner, but at sites such as the University of Rochester, Oak Ridge National

Laboratory, and the University of Chicago, all of which were part of a loosely coordinated effort overseen by the U.S. Atomic Energy Commission (AEC). In these experiments, conducted between 1945 and 1947, terminally ill patients were injected with plutonium-239, uranium, or polonium, often without their knowledge or informed consent. The stated purpose was to understand the biodistribution, excretion patterns, and retention times of these radioactive elements in the human body—information deemed crucial to the safety of workers in atomic bomb production facilities. While the scientific motivations were real, the methods violated fundamental ethical principles.

In contrast, the Donner Laboratory's work under John Lawrence was largely oriented toward therapeutic benefit rather than military risk assessment. The isotopes employed at Donner, such as phosphorus-32, iodine-131, and gold-198, were generally administered to patients with known cancers or hematologic disorders in an effort to relieve symptoms or slow disease progression. Many of these patients had exhausted conventional treatment options. While the research was experimental, and documentation of consent procedures from that era is often incomplete, there is a general consensus among historians that Donner's work was conducted with a more patient-centered ethos than some contemporaneous projects.

Nevertheless, the distinction is one of degree rather than kind. The concept of informed consent, as it is recognized today, was not codified in the 1940s. The Nuremberg Code—articulated in 1947 in the wake of Nazi medical atrocities—laid out the first formal ethical standards for human experimentation, but these principles were slow to take root in American biomedical practice. Many early clinical trials, including those at Donner, proceeded under paternalistic assumptions: that physicians and researchers were best positioned to decide what was in a patient's interest, and that full disclosure of experimental risks was either unnecessary or potentially harmful to the therapeutic relationship.

This context is important when evaluating the ethical posture of early nuclear medicine. While the researchers at Donner did not engage in the more egregious abuses seen in secret government experiments, they still operated in an

environment where transparency, autonomy, and accountability were insufficiently developed. Records from the period suggest that some patients may not have fully understood that they were receiving experimental treatments, or that they were part of a broader scientific study rather than routine medical care. These ambiguities complicate any retrospective judgment.

The long-term implications of these early ethical lapses were profound. Public revelations in the 1980s and 1990s—many of them the result of investigative journalism and Freedom of Information Act (FOIA) requests—led to national outrage and a reevaluation of the norms governing human subjects research. In 1994, the U.S. government formed the Advisory Committee on Human Radiation Experiments (ACHRE) to investigate these activities and issue recommendations. The committee's findings confirmed that a significant number of radiation experiments had been conducted without proper consent, and called for reforms in oversight, transparency, and participant compensation.

One of the most enduring legacies of this period has been the strengthening of ethical frameworks in biomedical research. Informed consent is now a cornerstone of clinical research, reinforced by institutional review boards (IRBs), patient advocacy protocols, and legal safeguards. The principles articulated in the Belmont Report (1979)—respect for persons, beneficence, and justice—are directly traceable to the moral reckoning prompted by early radiation studies. Furthermore, ongoing scrutiny of government-funded medical research ensures a higher level of accountability, even as new ethical challenges arise with emerging technologies like gene editing, artificial intelligence, and neuroenhancement.

From a historical perspective, the Donner Laboratory occupies a morally complex but comparatively less troubling space in the spectrum of radiation-era research. Its work represents the tension between urgent innovation and evolving ethics, between the promise of healing and the risks of experimentation. The fact that many of the therapeutic concepts tested at Donner later matured into widely accepted treatments—such as targeted radionuclide therapy and internal radiation—suggests that the underlying motivations were not exploitative, but exploratory.

In conclusion, the ethical reflections prompted by mid-century radiation research—including those conducted at and around Donner—serve as a cautionary tale and a moral compass. They remind us that scientific progress divorced from ethical accountability can easily veer into harm, and that the highest standards of care must always accompany the most advanced technologies. The patients of that era, whether knowingly or unknowingly involved, played an indispensable role in the development of modern medicine. Honoring their legacy means preserving the rights, dignity, and trust of every research subject who follows in their path.

10. Legacy and Modern Applications

The legacy of experimental radiation therapy research—particularly the pioneering work carried out at UC Berkeley’s Donner Laboratory—continues to shape and inspire some of the most advanced cancer treatments in use today. Although many of the early experiments were considered radical or even impractical at the time, they established a conceptual and technical foundation upon which modern precision radiation oncology is built. The trajectory from cyclotron-produced isotopes and neutron beams to today's proton therapy centers and internal radiation platforms illustrates how visionary science in high-risk contexts can evolve into mainstream clinical practice.

Among the most direct descendants of Donner-era innovations is proton therapy, now practiced in over 100 specialized centers worldwide. While the fundamental physics of proton beam therapy were well understood by the mid-20th century, the logistical and technical challenges of safe and reproducible clinical use delayed widespread adoption for decades. The early beam delivery trials at Berkeley, which tested the feasibility of using protons and later heavier ions (such as helium and carbon) to target deep-seated tumors, provided critical insights into beam shaping, range control, and biological response. Modern systems now integrate real-time imaging, multi-axis gantries, and sophisticated treatment planning algorithms, yet they still adhere to the Bragg peak principle first demonstrated in experimental protocols at Berkeley.

In parallel, the concept of using carbon ion beams—which offer even higher linear energy transfer (LET) and greater biological effectiveness than protons—has matured into a clinical reality, particularly in Germany, Japan, and China. These treatments are often reserved for radioresistant or deep-infiltrating tumors, such as certain sarcomas or head-and-neck cancers, where conventional X-rays fall short. The dosimetric precision and increased cytotoxicity of carbon ions derive directly from data first generated in the Bevalac-era experiments, in which helium, carbon, and even neon ions were tested in patients with complex tumor presentations. Today's heavy ion therapy facilities reflect not just a technological lineage, but an ideological commitment to treating cancer at the cellular and subcellular level with minimal harm to adjacent healthy tissues—a vision deeply rooted in Donner's approach to targeted radiobiology.

A second domain where the Donner Laboratory's influence remains strong is in Selective Internal Radiation Therapy (SIRT), also known as radioembolization. SIRT involves injecting radioactive microspheres—typically containing yttrium-90—into the hepatic artery to treat liver tumors. This technique grew out of earlier work with gold-198 and phosphorus-32 microspheres at Donner, which demonstrated the feasibility of delivering radiation from within the vascular system directly to tumor beds. Though early microsphere technology was primitive and delivery imprecise, it introduced the crucial concept of tumor-selective internal radiotherapy, which has since become a mainstay in interventional oncology. Advances in imaging, catheterization, and radiochemistry have since transformed this into a safe and effective therapy, but its conceptual origins trace directly back to the internal dosimetry work of mid-century pioneers.

The lasting impact of these experimental treatments on oncology extends beyond specific techniques. They helped to establish a new mindset: that radiation could be individualized, internalized, and intelligently deployed, rather than applied in bulk from external sources. This shift laid the foundation for subsequent developments in nuclear medicine and theranostics, such as the use of lutetium-177 in neuroendocrine tumors, or alpha-particle therapies in hematologic malignancies. Importantly, the early willingness to explore particle beams, isotopic

targeting, and sub-millimeter dosimetry opened the door to today's multi-modal, image-guided, and biologically optimized treatments.

However, the legacy of the Donner Laboratory is also methodological and philosophical. The laboratory operated in an environment where innovation was pursued aggressively, often at the edge of what was technically feasible and ethically understood. This high-risk, high-reward model produced both triumphs and missteps—but more critically, it illuminated the boundaries of possibility and pushed the field forward. The researchers who worked there did not ask merely how to treat tumors, but how to rethink the entire relationship between radiation, biology, and human health. Their work foreshadowed current trends in systems biology, personalized oncology, and even quantum medicine, where treatment is not limited to organ systems or anatomical targets, but focused instead on molecular and cellular precision.

Lessons from this history are profound:

- First, interdisciplinary collaboration—between physicists, engineers, chemists, and clinicians—is not optional but essential in tackling complex diseases like cancer.
- Second, pioneering innovation must be balanced by evolving ethical standards, ensuring that patients are protected even as new ground is broken.
- Third, technological limitations are often temporary, but foundational ideas endure. The Bragg peak, neutron capture, and internal dosimetry were once academic curiosities. Today, they are clinical tools.
- Finally, the Donner era teaches us that the courage to experiment—when guided by rigor, compassion, and a clear understanding of risk—can yield results far beyond what is initially imagined.

In this light, the legacy of experimental radiation therapy is not merely one of technical milestones, but of redefining the ambition of medicine itself: to heal with the precision of a physicist, the creativity of an engineer, and the responsibility of a physician. The ripple effects of those early efforts at UC

Berkeley continue to influence the direction of cancer therapy, reminding us that the future of medicine is often written by those willing to test the limits of the present.

11. Conclusion

The history of the Donner Laboratory at the University of California, Berkeley stands as one of the most consequential and emblematic chapters in the evolution of cancer treatment. Emerging from the crucible of nuclear physics and the invention of the cyclotron, Donner Lab became the first institutional setting in which particle physics was systematically integrated into human medicine. Its researchers, led by visionaries like John H. Lawrence, did not merely adapt existing tools to clinical problems—they invented entirely new paradigms, from the internal administration of radioactive isotopes to the development of high-energy particle beams as surgical alternatives. Their work laid the intellectual and technological foundations for much of what we now recognize as precision radiation oncology.

Through the pioneering use of phosphorus-32, neutron beams, helium and carbon ions, boron neutron capture therapy, radioactive microspheres, and attempts at magnetic targeting, the scientists and clinicians at Donner Lab tackled some of the most intractable challenges in cancer care. These innovations were not only technically ambitious but conceptually radical. They reframed the basic assumptions of how radiation could be used—not just as an external bludgeon, but as a finely tuned, biologically selective force capable of attacking tumors from within or directing destruction to the cellular and even subcellular scale. In doing so, the Donner group redefined both the possibilities and the boundaries of therapeutic radiation.

Yet for all its triumphs, the Donner Laboratory's legacy is also shaped by the moral and ethical tensions that accompanied its work. Operating in a time before formalized protocols of informed consent or standardized clinical oversight, many of its early studies existed in a gray zone—motivated by compassion and scientific

curiosity, but not always governed by the ethical frameworks now deemed essential. These complexities offer critical lessons for the present: that scientific ambition must always be matched by moral clarity, and that the rush to innovate must be tempered by a clear-eyed view of risk, human dignity, and long-term accountability.

As modern radiation oncology continues to evolve—with the advent of image-guided therapy, artificial intelligence, adaptive treatment planning, and biologically informed dose painting—the work of the Donner Laboratory remains deeply relevant. Today’s challenges, including how to optimize therapeutic ratio, how to reach previously inaccessible tumors, and how to individualize treatment based on biology rather than anatomy, were first confronted in experimental form by the physicists and physicians at Berkeley.

There are several key recommendations for contemporary practice that emerge from this historical reflection:

1. Preserve the spirit of interdisciplinary experimentation. Much of Donner’s success came from its refusal to silo knowledge. The fusion of nuclear physics, radiobiology, chemistry, and clinical medicine was not incidental—it was the engine of innovation. Radiation oncology today must maintain this ethos, especially as new frontiers like theranostics, radiogenomics, and quantum biology emerge.
2. Balance technological risk with ethical responsibility. The Donner Lab’s history shows the cost of rushing forward without adequate structures for patient consent and oversight. As we now develop tools capable of manipulating biological systems at increasingly fine scales, we must also develop ethical protocols that are as robust as our technical ones.
3. Honor conceptual boldness, but pursue technical refinement. The early methods at Donner were often crude, but the concepts—localized internal radiation, LET-based therapy selection, and in situ biological activation—were remarkably prescient. Modern tools can now deliver on these visions with much greater precision. We should continue to return to these

foundational ideas, refining them with the sophistication of today's technologies.

4. Document and revisit experimental failures as well as successes. The Donner era was filled with speculative experiments, some of which failed quietly or were abandoned due to technical limitations. Revisiting these ideas in light of contemporary tools—such as nanotechnology, molecular imaging, and real-time dosimetry—may open doors previously thought closed.

In the final analysis, the Donner Laboratory was more than a research facility—it was a crucible of radical scientific imagination. Its influence continues not only in the therapies used today but in the culture of inquiry, cross-disciplinary collaboration, and clinical boldness it inspired. If modern radiation oncology is to remain a frontier science—one that combines mathematical precision with biological insight and human compassion—it must carry forward the legacy of institutions like Donner: to see farther, to aim deeper, and to treat not just the disease, but the person within the particle field.

References

The following references represent a curated synthesis of archival documents, peer-reviewed literature, and oral histories that inform the historical, scientific, and ethical narrative presented in this paper. These sources, spanning from primary institutional records to scholarly assessments of radiation medicine's early development, provide a comprehensive foundation for understanding the legacy of the Donner Laboratory and its contributions to experimental cancer therapy.

Archival Materials

1. Donner Laboratory Archives, University of California, Berkeley – housed within the Bancroft Library and the Lawrence Berkeley National Laboratory (LBNL) historical collections. These include laboratory notebooks, internal reports, correspondence, treatment protocols, and grant proposals dating from the 1930s to the 1980s.
 2. Lawrence Berkeley National Laboratory Historical Archives – containing detailed information about the Bevatron, Bevalac, and early particle beam experiments. Includes blueprints, technical specifications, and patient treatment records (de-identified) from heavy ion therapy trials.
 3. U.S. Atomic Energy Commission (AEC) Reports – particularly those related to the Human Use Committees and isotope distribution programs. These reports are essential for understanding the policy context under which early medical isotope therapy developed.
 4. Advisory Committee on Human Radiation Experiments (ACHRE) Final Report, 1995. U.S. Government Printing Office. This report documents cases of non-consensual radiation experimentation and provides critical ethical evaluations of mid-century human research.
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This collection of references not only reflects the diverse and interdisciplinary nature of the Donner Laboratory's contributions but also supports critical reflection on how past innovations inform contemporary standards in radiation oncology. Researchers, clinicians, and historians alike can draw upon this legacy to navigate the ethical and technical frontiers that continue to define the future of cancer treatment.



Donner Laboratory, 1942.